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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte GREGORY ALAN LAZAR, ARTHUR J. CHIRINO, WEI DANG, JOHN RUDOLPH DESJARLAIS, STEPHEN KOHL DOBERSTEIN, ROBERT J. HAYES, SHER BAHADUR KARKI, and OMID VAFA

Appeal 2010-012556
Application 10/672,280
Technology Center 1600

Before ERIC GRIMES, LORA M. GREEN, and STEPHEN WALSH, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's rejection of claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142, and 144. We have jurisdiction under 35 U.S.C. § 6(b).

[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

STATEMENT OF THE CASE

Claims 88 and 89 are representative of the claims on appeal, and read as follows:

88. An antibody or immunoadhesin, said antibody or immunoadhesin comprising an amino acid substitution selected from the group consisting of 239D, 239E, 239Q, and 239T, wherein said antibody or immunoadhesin increases binding affinity to an FcγR as compared to its parent antibody or immunoadhesin, and wherein numbering is according to the EU index.

89. An antibody or immunoadhesin, said antibody or immunoadhesin comprising an amino acid substitution selected from the group consisting of 239D, 239E, 239N, 239Q, 239F, 239T, 239H and 239Y, wherein numbering is according to the EU index.

The following grounds of rejection are before us for review:

I. Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142, and 144[2] stand rejected under 35 U.S.C. § 103(a) as being rendered obvious by Presta.[3]

II. Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142, and 144 stand provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over copending Application Nos. 11/124,620;

[2] Appellants state that claims 88, 90, 98-102 (in part), 103-105, 106-112 (in-part), 137, 139, and 142-144 (in part) have been rejected (App. Br. 22). The Examiner responds that claims 91, 92, 94-102, 107, and 110 have been withdrawn from consideration (Ans. 4). Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142, and 144 were rejected in the Final Rejection (Final Rejection dated April 13, 2009), and we review the rejection as to those claims.

[3] Presta, US 6,737,056 B1, May 18, 2004.

11/396,495; 11/538,411; 11/544,165; 11/618,457; 11/618,472; 11/618,488; 11/765,353; and 11/765,390.

We affirm.

INITIAL MATTERS

Appellants appeal the Examiner's withdrawal of claim 90-92, 94-102, 107, 110, 141, and 143 as being drawn to a non-elected invention. (Appeal Br. 17-21). The propriety of the Examiner's restriction requirement is not an appealable issue but, rather is petitionable to the technology center director. *See* Manual of Patent Examining Procedure § 1002.02(c)(2) (8th ed., rev. 8, July 2010).

As to Rejection II, Appellants do not argue the merits of the rejection, but state that the rejection should be withdrawn if it is the only remaining rejection. As we are affirming the obviousness rejection over Presta, we also summarily affirm the obviousness-type double patenting rejections.

ISSUE (Rejection I)

Has the Examiner established by a preponderance of the evidence that Presta renders obvious the claimed antibody or immunoadhesin having a specified amino acid substitution at position 239?

FINDINGS OF FACT

FF1 The Examiner's statement of the rejection may be found at pages 5-6 of the Answer.

FF2 We adopt the Examiner's findings of fact and conclusions as our own.

FF3 We also note the following teachings of Presta.

FF4 Presta is drawn to "Fc region-containing polypeptides that have altered effector functions as a consequence of one or more amino acid modifications in the Fc region thereof" (Presta, col. 1, ll. 12-15).

FF5 Presta teaches further that the "binding site on human and murine antibodies for FcγR have been. . . mapped to the so-called 'lower hinge region' consisting of residues 233-239," of which "P238 and S239 have been cited as possibly being involved in binding, but these two residues have never been evaluated by substitution or deletion" (*id.* at col. 3, ll. 5-17).

FF6 Presta teaches a "polypeptide comprising a variant Fc region with altered Fc gamma receptor (FcγR) binding affinity," wherein the variant may comprise an amino acid modification at one or more of a number of amino acid positions, including position 239 (*id.* at col. 4, ll. 46-55).

FF7 Presta additionally teaches that the variant may display increased binding to one FcγR, such as FcγRIII, but decreased binding to a different FcγR, such as FcγRII (*id.* at col. 5, ll. 31-40).

FF8 Presta defines an "'amino acid substitution'" as the "replacement of at least one existing amino acid residue in a predetermined amino acid sequence with another different 'replacement' amino acid residue," wherein the replacement residue may be "'naturally occurring amino acid residues'" or "non-naturally occurring amino acid residues" (*id.* at col. 12, ll. 34-62).

FF9 Presta teaches further that the substitution may be a "'conservative substitution'" (*id.* at col. 19, ll. 47-65). As shown in Table 1 of Presta, one such preferred conservative substitution for serine (S) is threonine (T) (*id.* at col. 20).

FF10 Presta specifically discloses the S239A variant, and discloses that it has reduced binding to FcγRII and FcγRIII (*id.* at col. 57, Table 6).

FF11 Claim 13 of Presta recites:

> A polypeptide comprising a variant Fc region which is not a native sequence Fc region and has increased binding to an Fc gamma receptor (FcγR), which polypeptide comprises an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 255, 256, 258, 265, 267, 268, 269, 270, 272, 279, 280, 283, 285, 298, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 312, 315, 324, 327, 329, 330, 335, 337, 3338, 340, 360, 373, 376, 379, 382, 388, 389, 398, 414, 416, 419, 430, 434, 435, 437, 438 or 439 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat.

PRINCIPLES OF LAW

The Supreme Court has emphasized that "the [obviousness] analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007); *see also id.* at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. *Id.* at 417. Under the correct obviousness analysis, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420.

Objective evidence of nonobviousness (also called "secondary considerations") must always be considered in making an obviousness

determination, *Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 1538-39 (Fed. Cir. 1983), but it is not necessarily conclusive, *Ashland Oil, Inc. v. Delta Resins & Refrac., Inc.,* 776 F.2d 281, 306 (Fed. Cir. 1985). A "nexus" is a legally and factually sufficient connection between the objective evidence and the claimed invention, such that the objective evidence should be considered in the determination of nonobviousness. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.,* 851 F.2d 1387, 1392 (Fed. Cir. 1988). A "nexus" is required between the merits of the claimed invention and the evidence of secondary considerations in order for the evidence to be given substantial weight in an obviousness decision. *In re GPAC, Inc.,* 57 F.3d 1573, 1580 (Fed. Cir. 1995); *Stratoflex,* 713 F.2d at 1539. The burden of proving commercial success (and other types of secondary considerations, such as long felt need) during prosecution is on the applicant or patent owner. *See In re Huang,* 100 F.3d 135, 139-140 (Fed. Cir. 1996) ("In the *ex parte* process of examining a patent application … the PTO lacks the means or resources to gather evidence which supports or refutes the applicant's assertion that the sales constitute commercial success."). The burden of proving a nexus between the commercial success and the merits of the claimed invention during prosecution is also on the applicant or patent owner. *Huang,* 100 F.3d at 140 ("In sum, Huang simply has not carried his burden to prove that a nexus existed between any commercial success and the novel features claimed in the application.").

ANALYSIS

Appellants argue the claims in two groups, the first group comprised of those claims that are drawn to an antibody or immunoadhesin, wherein the claims recite that the antibody or immunoadhesin has increased binding affinity to an FcγR, and the second group comprised of those claims that do not recite that property (*see* App. Br. 40). We choose claim 88 as representative of the first group, and claim 89 as representative of the second group.

Appellants cite *Ex parte Watkins* (Appeal No. 2007-2523), asserting that even if it is non-binding opinion, it should be followed in this Appeal. We disagree. The rejection in *Watkins*, as acknowledged by Appellants, was an anticipation rejection under 102(e) (*see, e.g.*, App. Br. 24), and not an obviousness rejection as we have before us now. In addition, it involved a different residue, residue 280 (*see id.*). Thus, we find that the issues presented in the instant appeal are different from those in *Watkins*, and we decline to adopt the fact finding and reasoning set forth by the panel in *Watkins*.

Appellants argue further that there are 7 references in Presta "that teach that amino acid modifications at position 239 will decrease binding to FcγRs" (App. Br. 26; *see also id.* at 26-27). Appellants argue that the only reference to increased binding is claim 13, which Appellants assert was not part of the application as filed (*id.* at 28). Appellants assert:

> Taken together, the 7 references in the specification to decreased binding as a result of a change at position 239, weighed against a single reference that was not even part of the original disclosure, renders nonobvious claims directed to an

> antibody or immunoadhesin having increased binding as a result of a substitution at position 239.

(*Id.* at 29.)

Appellants cite *Takeda v. Alphapharm*, 492 F.3d 1350 (Fed. Cir. 2007) for the proposition that the closest prior art compound directed the ordinary artisan away from the claimed compound, and thus it would not have been "obvious to try" and modify the prior art compound to arrive at the claimed compound. *Id.* at 1359. Appellants argue that the ordinary artisan would not have chosen S239A as a lead compound in order to achieve better FcγR binding, as that variant had decreased binding to four of the five receptors tested, with the fifth receptor being similar to wild-type (App. Br. 30-31). Appellants argue further that Presta teaches "that different amino acid substitutions at the same position render dramatically different results" (*id.* at 31).

The claims are drawn to an antibody or immunoadhesin having a substitution at position 239. Thus, the claims are drawn to a compound (in this case a protein), or to a composition containing the protein. In this case, Presta specifically teaches that the serine at residue 239 may be substituted (FF6). Presta also teaches that threonine is the preferred substitution for serine (FF9). Thus, it would have been obvious to the ordinary artisan to substitute threonine for serine at position 239 (the claimed 239T substitution). In addition, as the properties of a compound cannot be separated from the compound, s*ee In re Papesch,* 315 F.2d 381, 391 (CCPA 1963) ("a compound and all of its properties are inseparable"), the S239T variant would inherently have the property of increased binding affinity to

an FcγR. As both claims 88 and 89 include the 239T variant, we conclude that the Examiner has set forth a prima facie case as to those claims. As Appellants only argued the claims in two groups, of which those claims are representative, the remaining claims stand or fall with those claims.

Moreover, as to the other variants encompassed by the claims, such as 239D, as noted by the Examiner, Presta teaches that position 239 may be substituted with another naturally occurring amino acid, and also teaches methods for determining binding to FcγR (*see* Ans. 6). In addition, the patent also specifically claims a variant at position 239 that has increased binding to a FcγR (FF11). As "[a] patent shall be presumed valid," 35 U.S.C. § 282, we agree with the Examiner that it would have been obvious to substitute the serine at position 239 with other naturally occurring amino acids and screen for the desired activity with a reasonable expectation of success of obtaining variants with increased binding to a FcγR. *See In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988) (noting that all that is required is a reasonable expectation of success, not absolute predictability of success).

Thus, the instant appeal is distinguishable from *Takeda*, which dealt with thiazolidine derivatives useful as antidiabetic agents, *Takeda*, 492 F.3d at 1353, wherein the court found there was no reason to modify the prior art compound to arrive at the compound at issue, *id.* at 1357. In the instant appeal, as discussed above, Presta suggests modifying the serine at position 239, and also notes that the substitution of threonine for serine is a preferred, conservative substitution.

Appellants further argue that the Examiner has failed to make the factual inquiries as required by *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966) of (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of nonobviousness, if any (App. Br. 32-33). First, Appellants argue that the Examiner has made no findings as to the level of ordinary skill in the art (*id.* at 33-34). Second, as to the scope and content of the prior art, Appellants argue that Presta "does not teach the claimed species position 239 having the required functional limitation," and reiterate that the mutation made at that position had reduced binding to FcγR (*id.* at 34). Third, as to the differences between the claimed invention and the prior art, Appellants argue that "Presta does not teach any substitutions at position 239 that enhance binding to an FcγR" (*id.* at 35).

As to the level of skill of the ordinary artisan, Presta, as cited by the Examiner is the best evidence. As discussed above, Presta teaches that one can make substitutions at position 239, and that those substitutions may be with one of the 20 (19, without cysteine) naturally occurring amino acids. Presta also teaches how to screen for binding to a FcγR. And thus, Presta demonstrates that it would have been well within the level of skill of the ordinary artisan to substitute the serine at position 239 with another amino acid, and test for binding to a FcγR. We note further that certain substitutions may have increased binding to one FcγR, but may also have deceased binding to a different FcγR.

As to Appellants' argument that Presta does not teach the claimed species position 239 having the required functional limitation, claim 13 of

Presta recites a polypeptide having a variant Fc region that has increased binding to a FcγR, wherein the position that has a modification is 239. Moreover, as discussed above, the 239T substitution would be a preferred substitution, and would have inherently had that property.

Appellants argue finally that there are secondary indicia of non-obviousness (App. Br. 39). Appellants argue that the Fc technology, including variants at position 239, have enjoyed commercial success, and has been licensed to various companies, such as MedImmune (*id.*). Appellants argue further:

> In fact, with specific reference to position 239, the Appellants respectfully point out that MedImmune is actually utilizing some of these variants, as evidenced by U.S. Publication No. 2008/0071063, claims 13-16, with specific 239 residues recited, including 239E, 239D, 239Q, 239N, 239F, 239T, 239H and 239Y (claim 14) and 239D (claim 16); Protein Design Labs as evidenced by WO 05102387A2, pages 50-51, with 239D, 239E, 239N, 239Q, 239F, 239T, 239H, and 239Y specifically recited at page 50, lines 13-14; and Chugai as evidenced by U.S. Publication No. 2007/0087005, claims 3 -5, 9 and 10, with specific 239 residue aspartic acid (D) recited.

(*Id.* at 39-40.)

Appellants' arguments are again not convincing. As to the fact that the Fc technology has been licensed to several companies, Appellants have not established a nexus between the claims at issue in the instant appeal and the licensing of "Fc technology" in general. As to the issue that other companies are utilizing the technology as evidenced by different patent applications and publications, Appellants have not established that the technology was obtained from them. In fact, as evidenced by Presta, the art

demonstrated that one could modify the Fc region to obtain polypeptides having modified binding to FcγRs.

CONCLUSION OF LAW

We conclude that the Examiner has established by a preponderance of the evidence that Presta renders obvious the claimed antibody or immunoadhesin having a specified amino acid substitution at position 239. We thus affirm the rejection of 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142, and 144 under 35 U.S.C. § 103(a) as being rendered obvious by Presta.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

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